

The University of Chicago

HYDROGEN-DEUTERIUM EXCHANGE IN ETHYL ESTERS

A DISSERTATION SUBMITTED TO THE FACULTY
OF THE DIVISION OF THE PHYSICAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF DOCTOR
OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

1938

By
KENNETH EBERLY

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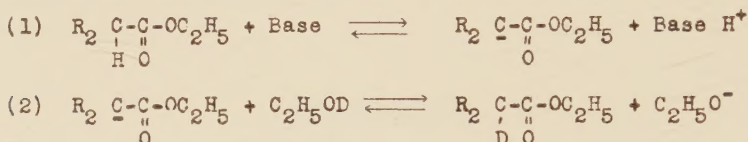


ACKNOWLEDGMENT

The author is greatly indebted to Dr. Weldon G. Brown and to Dr. M. S. Kharasch for invaluable advice and patience during the course of this research.

INTRODUCTION

Since deuterium oxide has become available, a general method of determining the number of labile hydrogen atoms in compounds has presented itself. The method consists of determining whether an exchange of hydrogen and deuterium atoms occurs when two compounds of different isotopic composition are brought together in solution. This research deals with the isotopic exchange of the alpha hydrogen atoms in aliphatic esters with deuterioalcohol (C_2H_5OD) in the presence of a basic catalyst. The reaction may be represented schematically as follows.



As the "alpha carbon effect" may be transferred through a vinyl connection,¹ exchange reactions of compounds of the type $H_3C-CH=CH-COOC_2H_5$ were also investigated.

The work of Sprowls² indicated that the simpler aliphatic esters and deuterioalcohol do not undergo hydrogen-deuterium exchange in the presence of small amounts of sodium hydroxide. As sodium ethylate is the strongest base that can exist in ethyl alcohol, its catalytic properties were examined, and it was found to be capable of bringing about the hydrogen-deuterium exchange between an aliphatic ester and deuterioalcohol. However, isotopic exchange between the malonic esters and deuterioalcohol may be effected by the presence of a base as weak as sodium salicylate.

The exchange reactions are related to the Claisen condensation of esters in the respect that an ester anion must presumably first be formed by the action of the base on the ester itself. Both the exchange reactions and the Claisen condensation of esters

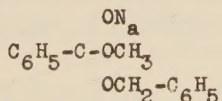
¹Fuson, "Principles of Vinology," Chem. Rev., **16**, 1-27 (1935).

²Sprowls (Unpublished Ph.D. dissertation, University of Chicago, 1938).

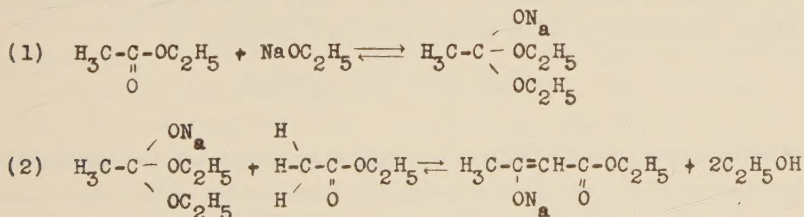
require alpha hydrogen and sodium ethylate. One objective of this research was to find a correlation between the exchange in esters and the Claisen condensation.

It is a well-known fact that isovaleric ester and esters of the acetic series containing only one alpha hydrogen atom fail to undergo the Claisen condensation in the presence of sodium ethylate. These compounds will, however, condense in the presence of a stronger base such as sodium triphenylmethyl¹ or mesityl magnesium bromide. The failure of these esters to condense is supposedly due to the low lability of the alpha hydrogen atoms in these compounds. The rate of hydrogen-deuterium exchange under comparable conditions is in agreement with this supposition. However, the failure of these esters to condense may be due in part to other factors involving the relative reactivities of the anion and of the ester with which it condenses. It is known that ethyl acetate condenses with the carbethoxy group of ethyl oxalate with much greater ease than it condenses with the carbethoxy group of ethyl benzoate.

The subject of the mechanism of the Claisen condensation of esters has been one of much controversy. A brief review of some of the mechanisms of the Claisen condensation will be presented at this point. Claisen was convinced that at least two alpha hydrogen atoms were necessary in the ester in order that it be able to undergo the condensation. Considering the fact that sodium benzyolate adds to methyl benzoate to form the addition compound



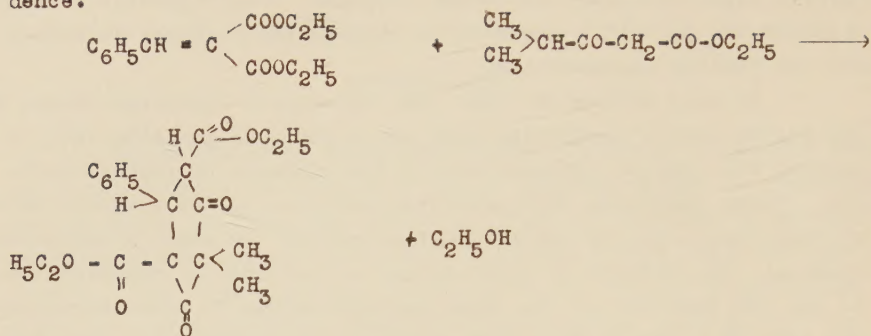
Claisen suggested a mechanism based on the following reactions.



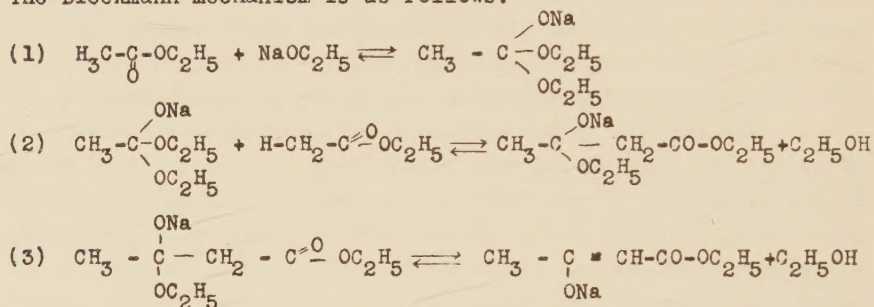
Dieckmann endeavored to show that only one alpha hydrogen atom is necessary to effect a condensation with the following evi-

¹Hauser, and Renfrow, J. Am. Chem. Soc., **59**, 1823 (1937).

dence.

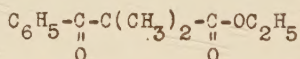


After the initial condensation, however, another alpha hydrogen atom is necessary to form the enolic form of the beta keto ester. The Dieckmann mechanism is as follows.¹



Scheibler proposed that the sodium salt of the enolic form of the ester is the intermediate in the Claisen condensation of an ester.²

Recently Hauser and Renfrow have succeeded in the formation of a beta keto ester from ethyl isobutyrate by the employment of sodium triphenylmethyl.³ Later they succeeded in condensing ethyl isobutyrate with ethyl benzoate forming



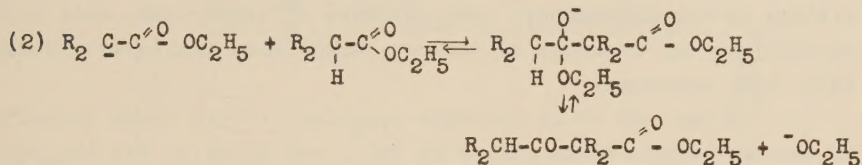
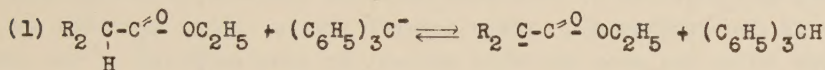
a compound which is unique among ester condensation products in

¹Dieckmann, Ber., 33, 2670 (1900).

²Scheibler and Ziegner, Ber., 55, 739 (1922).

³Hauser, and Renfrow, J. Am. Chem. Soc., 59, 1823 (1937).

containing neither alpha nor gamma hydrogen atoms.¹ In consideration of their results, these authors have prepared the following mechanism.



EXPERIMENTAL PART

Procedure

In order to determine the number of exchangeable hydrogen atoms in an ester, a reaction mixture consisting of deuterioalcohol of known deuterium content, ester, and a basic catalyst was made up. In all cases 5 cc. of the standardized solution of deuterioalcohol was used. The best results were obtained when the sodium ethylate from approximately 40 milligrams of sodium dissolved in the deuterioalcohol was employed as a catalyst. Smaller amounts of sodium ethylate gave entirely unsatisfactory results. After a given period of reaction, either the alcohol or the ester was isolated and its deuterium content determined.

The deuterioalcohol was prepared from pure, anhydrous ethyl alcohol and deuterium oxide according to the method of Kharasch, Brown, and McNab.² Anhydrous ethyl alcohol was prepared according to Noyes.³

When exchange reactions were to be carried out at elevated temperatures, the reactants were placed in a tube, the whole cooled to $-80^\circ\text{C}.$, then the air removed by a vacuum pump. The tube was then sealed off, removed from the cooling bath, and placed in a bath maintained at the desired temperature. If, however, the reaction was to take place at room temperature or lower, the reactions

¹Renfrow, and Hauser, J. Am. Chem. Soc., **60**, 463 (1938).

²Kharasch, Brown, and McNab, J. Org. Chem., **2**, 39 (1937).

³Noyes, J. Am. Chem. Soc., **45**, 861 (1923).

were carried out in stoppered test tubes.

Special attention was paid to the experiments involving diphenylacetic ester as it is a solid. It had to be dissolved in a solvent previous to treatment with the solution of sodium ethylate in deuteroalcohol. After several trials, ethyl benzoate was found to be the most suitable solvent in consideration of the conditions of the experiment. For purposes of comparison, data were obtained on the exchange of related esters when similarly diluted with ethyl benzoate.

At the end of an exchange reaction, it was found convenient to recover esters which boiled at 150 C. or lower by salting out. The reaction mixture was shaken four successive times with a 20% solution of sodium chloride; and the ester so isolated was dried over anhydrous sodium sulphate, filtered, and distilled. At this stage the ester was ready for the determination of its deuterium content.

For the esters of high boiling point, it was found convenient to recover the alcohol for deuterium analysis by fractional distillation of the reaction mixture after having destroyed the catalyst by either carbon dioxide or phosphorus pentoxide.

The deuteroalcohol or deuteroester was analyzed for deuterium as follows. About 1.5 cc. of the liquid was burned by means of a sintered glass wick in a stream of dry air, the water formed being collected in a glass trap cooled by a bath of dry ice and methanol. The combustion apparatus is illustrated in Figure 1. On completion of the combustion the ice in the trap was allowed to melt, and the resulting water was pipetted into a glass capsule containing 100 milligrams of potassium permanganate and 20 milligrams of sodium carbonate. The capsule was then sealed off and heated for one hour at 180 C. to insure complete oxidation of any organic matter in the water sample.

After cooling, the contents of the capsule were transferred to a vacuum distillation apparatus illustrated in Figure 2. Two successive vacuum distillations were made, the final distillate being collected in the detachable float tube. When the contents of the float tube were completely liquified, dry atmospheric air was admitted to the system. At this stage the water was ready for the deuterium analysis by the float-temperature method.

A calibrated quartz float was first introduced into the water in the float tube, followed by a thermometer graduated in

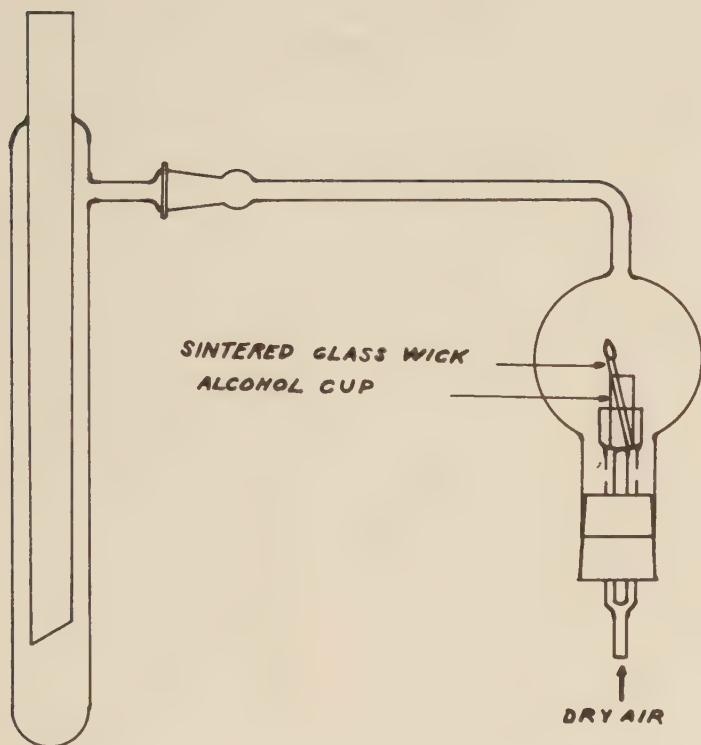


Fig. 1.--Combustion apparatus

0.1°C. The whole was then immersed in a variable temperature bath, the set-up illustrated by Figure 3. The temperature of the bath was then so adjusted that the quartz float neither rose nor sank. This temperature will be referred to as the "floating temperature." The movement of the float was observed with the aid of a cathetometer.

The quartz float was calibrated by observing the floating temperatures of samples of water of known deuterium content. A calibration curve for the float was constructed by plotting the mole-percentages of D_2O in the water samples versus the corresponding floating temperatures. A table showing the composition of the water samples and the corresponding floating temperatures is given below.

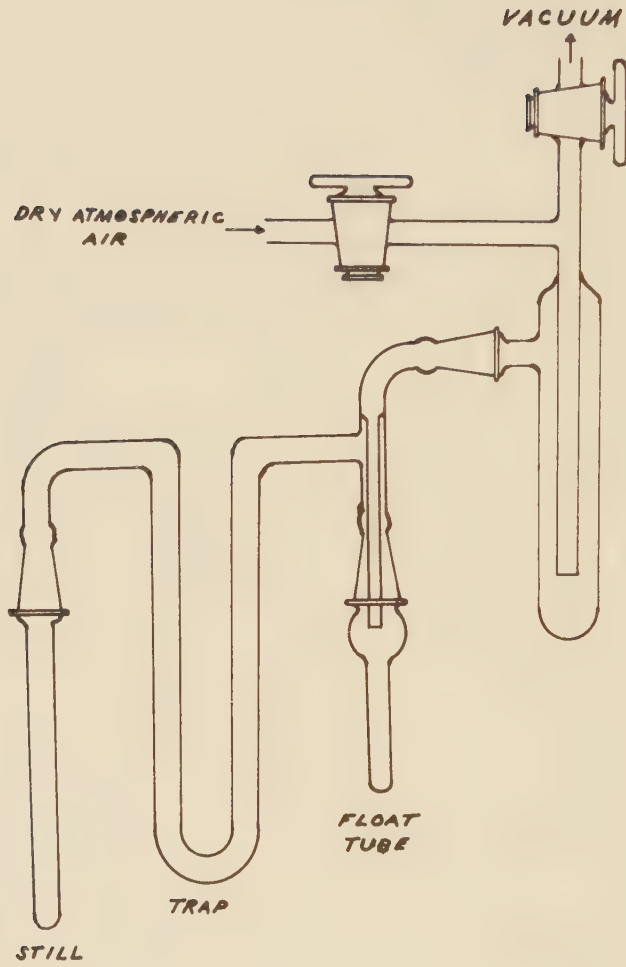


Fig. 2.--Vacuum distillation apparatus

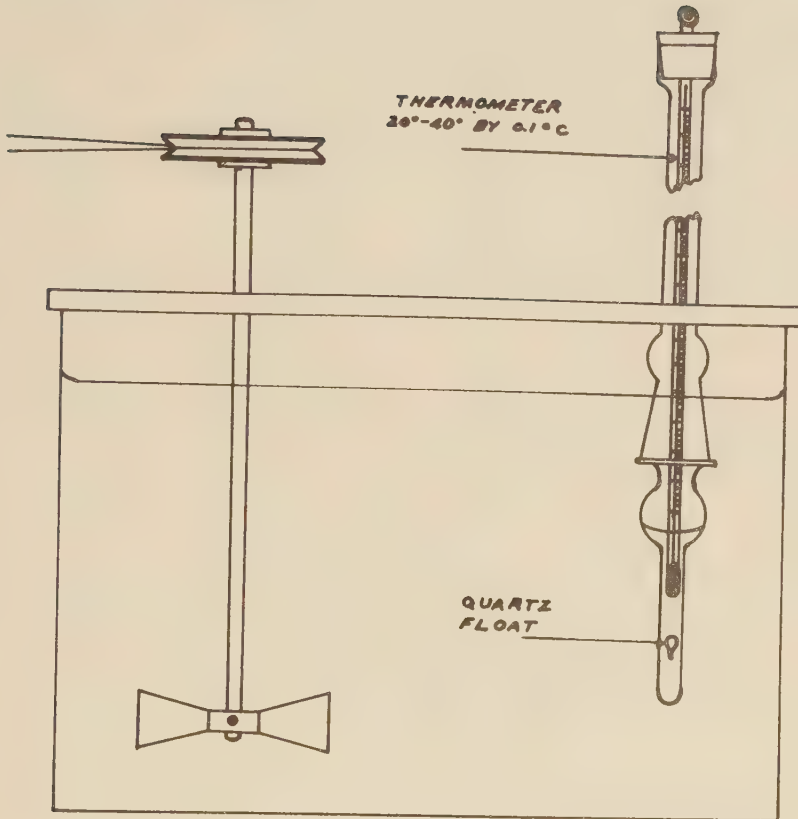


Fig. 3.--Flotation apparatus

TABLE I
CALIBRATION OF THE FLOAT

Weight of 12.13 Mole % D ₂ O (gms.)	Weight of H ₂ O added (gms.)	Mole Fraction of D ₂ O	Floating Temperature
.....		0	23.79°C.
2.1093	48.216	0.005020	25.94°C.
3.4580	46.6705	0.008266	27.29°C.
4.4827	47.270	0.010381	28.04°C.
5.7436	42.674	0.014224	29.50°C.
4.1484	20.8987	0.01987	31.46°C.
5.8833	19.7028	0.02761	34.01°C.
7.3788	18.5591	0.03413	35.82°C.

The quartz float was kept in concentrated nitric acid while not in use. Before making a run, the float was washed about ten times with water distilled from potassium permanganate, then allowed to dry in a desiccator.

Calculation of Results

The experimental results are expressed in terms of "exchange number," calculated by means of the following relation.

$$\frac{\frac{\text{amount of deuterium in ester}}{\text{moles of ester}}}{\frac{\text{amount of deuterium in alcohol}}{\text{moles of alcohol}}} = \text{exchange number}$$

The exchange number should approach as a limit the theoretical number of labile hydrogen atoms in the molecule under the assumption of statistical distribution. The data contained in the column headed "percentage exchange" in the table of results show to what extent this theoretical limit is approached.

Preparation of the Esters

Many of the esters were of commercial grade and were purified by fractional distillation before use. In other instances the organic acids were available, and the esters were prepared by refluxing the respective organic acids with an excess of absolute ethyl alcohol in the presence of a small amount of either hydrogen

chloride or concentrated sulphuric acid. Still other esters had to be synthesized from more readily available materials, and the references to their preparation are listed in the following table.

TABLE 2

Ethyl Ester	Boiling Point	Pressure In mm. Hg.	Source or Reference
Acetic	77°C.	750	Eastman Kodak Co.
Propionic	99°C.	750	Eastman Kodak Co.
Butyric	120-121°C.	750	Eastman Kodak Co.
Isobutyric	110-112°C.	750	Eastman Kodak Co.
Isovaleric	135°C.	750	Eastman Kodak Co.
Lauric	268-271°C.	750	Prepared from acid
Stearic	201-206°C.	13	Prepared from acid
Cyclohexylacetic ...	208°C.	750	1
Methoxypropionic ..	134-137°C.	750	2
Dimethylaminoacetic.	149-151°C.	750	3, 4
Phenylacetic	222°C.	740	Eastman Kodak Co.
Diphenylacetic	M.P.=58°C.	...	Prepared from acid
Methoxyphenylacetic	250-255°C.	748	5
Hydratropic	224-227°C.	741	6, 7, 8, 9, and 10
Malonic	198°C.	750	Eastman Kodak Co.
Methylmalonic	193-194°C.	740	11

¹Freundler, and Damond, Chem. Zentr., 2, 1430 (1905).

²Purdie, and Lauder, J. Chem. Soc., 73, 869 (1898).

³Willstätter, Ber., 35, 599 (1902).

⁴Beilstein, "Handbuch der Chemie," 4th ed., IV, 384.

⁵McKenzie, J. Chem. Soc., 75, 755 (1899).

⁶Wislicenus, Ber., 27, 1093 (1894).

⁷Wislicenus, Ber., 28, 816 (1895).

⁸Conrad and Limpach, Ann., 192, 153 (1878).

⁹Conrad and Limpach, Ann., 204, 129 (1880).

¹⁰Wheeler, J. Am. Chem. Soc., 24, 686 (1902).

¹¹Conrad and Limpach, Ann., 204, 134 (1880).

TABLE 2--Continued

Ethyl Ester	Boiling Point	Pressure In mm. Hg.	Source or Reference
Phenylmalonic	171°C.	21	Abbott Laboratories
Trans-Crotonic	135-136°C.	744	Prepared from acid
Dimethylacrylic	152-155°C.	744	1
Sorbic	193-196°C.	747	Prepared from acid
Citraconic	225-225.5°C.	748	2,3
Mesaconic	223-225°C.	748	4
o-Toluic	221-223°C.	739	Prepared from acid
p-Toluic	228-229°C.	740	Prepared from acid

¹Barrier, Bull. Soc. Chim. (3), 33, 815 (1905).

²Organic Syntheses, 11, 70.

³Ibid., 28.

⁴Ibid., 74.

Mesitylenecarboxylic ethyl ester was not described in the literature. The preparation of it was carried out by refluxing the silver salt of the acid with ethyl iodide. The mesitylenecarboxylic acid was prepared according to the method of Bamford and Simonsen.¹ The silver salt of mesitylenecarboxylic acid is quite insoluble in cold water, therefore it was prepared by treating a solution of ammonium mesitylenecarboxylate with an excess of silver nitrate. The silver salt was separated by filtration and dried at 110°C., then it was refluxed with a slight excess of ethyl iodide using absolute ethyl alcohol as a solvent. After the mixture had refluxed two hours, the liquid was separated from the silver iodide by filtration. The alcohol and excess ethyl iodide were removed from the filtrate by distillation, and the residual liquid fractionated under reduced pressure. On refractionation a product distilling between 150-152°C. at a pressure of 32 mm. was obtained.

The ester boiled at 251-252°C. at a pressure of 747 mm. The specific gravity of the ester at 28°C as compared with water at 20°C. was 0.974. When the ester was saponified, mesitylenecarboxylic acid (m.p. = 153°C) was obtained. On treating 0.5 grams of the ester with a mixture of 1 cc. of concentrated nitric acid and 2 cc.

¹Bamford, and Simonsen, J. Chem. Soc., 97, 1906 (1910).

TABLE 3

EXCHANGE IN ETHYL ESTERS

No.	Ester	Ester (moles)	Ini- tial Alco- hols	Catalyst (milligrams.)	Reac- tion Temp. (°C.)	Reaction Time (Hours)	Experi- mental Proce- dure ^b	Mole % D ₂ O from Re- covered Liquid	Ex- change Number	Remarks
1.	Acetic	0.0511	1	27.8 Na	110	140.5	1	2.673	2.12	
2.	Acetic	0.0511	1	13.8 Na	110	123.5	1	2.780	2.30	
3.	Acetic	0.0511	1	46.7 Na	110	1.0	1	2.700	2.20	
4.	Propionic ...	0.0436	1	5.0 Na	110	69.0	1	0.113	0.05	Insufficient cat- alyst
5.	Propionic ...	0.0436	1	16.0 Na	110	170.0	1	0.240	0.11	Insufficient cat- alyst
6.	Propionic ...	0.0436	1	42.1 Na	110	143.0	1	2.080	1.70	
7.	Propionic ...	0.0436	1	43.3 Na	110	20.0	1	2.125	1.77	
8.	Propionic ...	0.0436	1	32.9 Na	110	1.0	1	2.110	1.74	
9.	Butyric	0.0378	1	5.0 Na	110	114.0	1	0.068	0.04	Insufficient cat- alyst
10.	Butyric	0.0378	1	13.3 Na	110	165.0	1	0.080	0.04	Insufficient cat- alyst
11.	Butyric	0.0378	1	32.1 Na	110	142.0	1	1.867	1.73	
12.	Butyric	0.0378	1	35.6 Na	110	1.0	1	1.874	1.73	
13.	Isobutyric ..	0.0375	1	5.0 Na	110	68.0	1	0.047	0.03	Insufficient cat- alyst
14.	Isobutyric ..	0.0375	1	17.6 Na	110	168.0	1	1.270	0.92	
15.	Isobutyric ..	0.0375	1	32.2 Na	110	142.0	1	1.240	0.91	
16.	Isobutyric ..	0.0375	1	39.1 Na	110	1.0	1	1.234	0.90	
17.	Dimethyl- aminoacetic.	0.0400	v	45.8 Na	25	4.0	111	1.345	1.984	Alcohol redistilled with P ₂ O ₅
18.	Dimethyl- aminoacetic.	0.0400	v	None	25	4.0	1v	2.503	0.085	Self-catalyzed, Distilled in vacuo at 25° C.
19.	Phenylacetic.	0.03134	1	15.0 Na	110	90.0	1v	2.810	1.04	

TABLE 3--Continued

No.	Ester	Ester (moles)	Initial Alcohol	Catalyst (milligrams.)	Reaction Temp. (°C.)	Reaction Time (Hours)	Experimental Procedure	Mole % D ₂ O from Re-covered Liquid	Exchange Number	Remarks
20.	Phenylacetic.	0.03134	I	14.7 Na	110	163.0	iv	3.340	0.42	Distilled in vacuo at 25°C.
21.	Phenylacetic.	0.03134	I	31.8 Na	110	89.0	iv	2.250	1.91	
22.	Phenylacetic.	0.03134	I	32.1 Na	25	1.0	iv	2.320	1.76	
23.	Phenylacetic.	0.02082	II	43.9 Na	26	1.0	iv	1.870	2.70	Failure to remove xylol quantitatively from alcohol
24.	Phenylaceticd	0.02082	II	42.1 Na	22	1.0	iv	2.097	1.98	
25.	Phenylacetic.	0.03134	II	41.8 Na	23	1.0	II	1.938	1.875	
26.	Phenylaceticd	0.02082	II	40.0 Na	0	0.5	II	2.125	1.997	
27.	Diphenyl-aceticc	0.02082	II	43.9 Na	26	1.0	iv	2.007	2.25	Alcohol not free of xylol
28.	Diphenyl-aceticd	0.02082	II	42.1 Na	22	1.0	iv	2.470	1.07	
29.	Phenylmalonic	0.0230	V	None	25	0.0167	iv	2.600	None	
30.	Phenylmalonic	0.0230	V	40.0 Na	0	0.0333	II	2.033	1.01	
31.	Phenylmalonic	0.0230	V	40.0 Sodium Sali-cylate	25	95.25	iv	2.001	1.11	Vacuum distilled in two hours at 25° C.
32.	Phenylmalonic	0.0230	V	40.0 Sodium Sali-cylate	25	97.33	iv	2.004	1.11	Vacuum distilled in two hours at 25° C.

TABLE 3--Continued

No.	Ester	Ester (moles)	Initial Alcohol	Catalyst (milligrams.)	Reaction Temp. (°C.)	Reaction Time (Hours)	Experimental Procedure	Mole % D ₂ O from Recovered Liquid	Exchange Number	Remarks
33.	Dimethyl-acrylic	0.0360	v	41.0 Na	110	211.0	ii	2.120	5.45	

^aAll reaction mixtures were made up with 5 cc. of deuterioalcohol (0.08526 moles). Six different batches of deuterioalcohol were used, the composition of which is given as follows in terms of D₂O content of water of combustion: i = 3.850 mole %; ii = 3.132 mole %; iii = 3.032 mole %; iv = 2.726 mole %; v = 2.603 mole %; vi = 2.390 mole %. In calculating the results, allowance was made for the alcohol removed by the reaction with the sodium.

^bThe experimental procedure varied according to whether the ester or the alcohol was recovered for the analysis and according to the manner of destroying the catalyst. The procedure is referred to as follows: i = ester recovered by salting out; ii = alcohol recovered by distillation, catalyst destroyed by addition of solid CO₂; iii = alcohol recovered by distillation, catalyst destroyed by addition of equivalent amount of P₂O₅; iv = alcohol recovered by distillation, catalyst not destroyed.

^cReaction mixture contained 5 cc. of xylol.

^dReaction mixture contained 5 cc. of ethyl benzoate.

TABLE 4

RATE OF EXCHANGE IN ETHYL ESTERS

No.	Ester	Ester (moles)	Initial Alcohol ^a	Catalyst (milligrams.)	Reac- tion Temp. (°C.)	Reaction Time (Hours)
34.	Acetic	0.0511	i	44.1 Na	25	1.0
35.	Acetic	0.0511	ii	36.9 Na	25	4.0
36.	Acetic	0.0511	vi	40.0 Na	25	16.0
37.	Acetic	0.0511	vi	40.0 Na	25	1.0
38.	Acetic	0.0511	vi	40.0 Na	25	4.0
39.	Acetic	0.0511	vi	40.0 Na	25	16.0
40.	Propionic	0.0436	i	35.7 Na	25	1.0
41.	Propionic	0.0436	ii	36.9 Na	25	4.0
42.	Propionic	0.0436	vi	40.0 Na	25	16.0
43.	Butyric	0.0378	i	38.4 Na	25	1.0
44.	Butyric	0.0378	ii	36.9 Na	27	4.0
45.	Butyric	0.0378	vi	40.2 Na	25	16.0
46.	Lauric	0.0370	v	40.5 Na	25	4.0
47.	Lauric	0.0370	v	40.5 Na	25	4.0
48.	Stearic	0.0370	v	40.8 Na	25	4.0
49.	Isobutyric	0.0375	i	42.6 Na	25	1.0
50.	Isobutyric	0.0375	ii	36.9 Na	25	4.0
51.	Isobutyric	0.0375	vi	39.7 Na	25	16.0
52.	Isovaleric	0.0335	ii	36.9 Na	25	1.0
53.	Isovaleric	0.0335	ii	36.9 Na	25	4.0
54.	Isovaleric	0.0370	v	40.8 Na	25	4.0
55.	Isovaleric	0.0370	vi	39.8 Na	25	16.0
56.	Cyclohexylacetic.	0.0370	v	40.7 Na	25	4.0
57.	Cyclohexylacetic.	0.0370	v	40.4 Na	25	4.0
58.	Methoxypropionic	0.0436	ii	41.6 Na	24	4.0

TABLE 4--Continued

No.	Experimental Proce- dure ^b	Mole % D ₂ O from Recov- ered Liquid	Exchange Number	Percent- age Ex- change	Remarks
34.	1	0.954	0.41	13.7	
35.	1	1.705	1.302	43.4	
36.	1	1.430	1.560	52.0	Violent initial shaking, caus- ing immediate precipitation
37.	1	0.430	0.281	9.4	Violent initial shaking, caus- ing immediate precipitation
38.	1	0.780	0.593	19.8	Violent initial shaking, caus- ing immediate precipitation
39.	1	1.464	1.634	54.5	Violent initial shaking, caus- ing immediate precipitation
40.	1	0.243	0.111	5.5	
41.	1	0.283	0.235	11.8	
42.	1	0.612	0.549	27.5	
43.	1	0.063	0.035	1.8	
44.	1	0.177	0.114	5.7	
45.	1	0.383	0.370	18.5	
46.	11	2.478	0.114	5.7	
47.	11	2.483	0.109	5.5	
48.	11	2.504	0.0902	4.5	
49.	1	0.025	0.0116	1.2	
50.	1	0.030	0.017	1.7	
51.	1	0.040	0.034	3.4	
52.	1	0.050	0.034	1.7	
53.	1	0.067	0.050	2.5	
54.	1	0.056	0.0514	2.6	
55.	1	0.094	0.0955	4.3	
56.	11	2.500	0.093	4.7	
57.	11	2.500	0.093	4.7	
58.	1	0.0425	0.027	2.7	

TABLE 4--Continued

No.	Ester	Ester (moles)	Initial Alcohol ^a	Catalyst (milligrams.)	Reac- tion Temp. (°C.)	Reaction Time (Hours)
59.	Methoxypropionic	0.0370	v	40.2 Na	25	4.0
60.	Phenylacetic ^c ...	0.02082	11	40.3 Na	0	0.0833
61.	Phenylacetic ^d ...	0.02082	11	40.6 Na	0	0.0833
62.	Phenylacetic ^c ...	0.0100	111	40.5 Na	0	0.0833
63.	Diphenylacetic ^c ..	0.02082	11	40.6 Na	0	0.0833
64.	Diphenylacetic ^d ..	0.02082	11	40.4 Na	0	0.0833
65.	Diphenylacetic ^c ..	0.0100	111	40.4 Na	0	0.0833
66.	Methoxyphenyl- acetic ^c	0.02082	11	40.8 Na	0	0.0833
67.	Methoxyphenyl- acetic ^c	0.0100	111	40.5 Na	0	0.0833
68.	Hydratropic ^c	0.02082	111	40.6 Na	0	0.0833
69.	Phenylmalonic ...	0.0230	v	5.0 Sodium Salicylate	25	1.0
70.	Phenylmalonic ...	0.0230	v	5.0 Sodium Salicylate	25	4.0
71.	Methylmalonic ...	0.0230	v	5.0 Sodium Salicylate	25	4.0
72.	Malonic	0.0230	v	5.0 Sodium Salicylate	25	4.0
73.	Trans-Crotonic ..	0.0370	1v	39.3 Na	25	4.0
74.	Dimethylacrylic	0.0360	v	40.0 Na	27	4.0
75.	Sorbic	0.0370	1v	40.0 Na	25	4.0
76.	Citraconic	0.0370	1v	39.8 Na	25	4.0
77.	Mesaconic	0.0370	1v	40.4 Na	25	4.0
78.	o-Toluic	0.0315	v	40.0 Na	110	16.0

TABLE 4--Continued

No.	Experi- mental Proce- dure	Mole % D ₂ O from Recov- ered Liquid	Exchange Number	Percent- age Ex- change	Remarks
59.	1	0.044	0.035	3.5	
60.	11	2.617	0.790	39.5	
61.	11	2.510	0.994	49.7	Final alcohol not free from tetralin
62.	11	2.734	0.910	45.5	
63.	11	2.846	0.403	40.3	Reagents insufficiently cooled; supersaturated solution
64.	11	2.964	0.227	22.7	Some tetralin in the al- cohol; supersaturated solution
65.	11	2.943	0.253	25.3	
66.	11	3.002	0.176	17.6	
67.	11	2.972	0.1685	16.9	
68.	11	2.937	0.1297	13.0	
69.	1v	2.440	0.246	24.8	Vacuum distilled in two hours at 25°C.
70.	111	2.387	0.335	33.5	
71.	111	2.437	0.252	25.2	
72.	111	1.780	1.714	85.7	
73.	1	0.813	0.635	21.2	
74.	1	0.393	0.348	5.8	
75.	11	2.504	0.200	6.7	
76.	11	2.023	0.784	26.1	
77.	11	2.640	0.0735	2.4	
78.	11	2.560	0.045	1.5	Calculated for 3 ex- changeable hydrogen atoms

TABLE 4--Continued

No.	Ester	Ester (moles)	Initial Alcohol ^a	Catalyst (milligrams.)	Reaction Temp. (°C.)	Reaction Time (Hours)
79.	p-Toluic	0.0312	v	40.3 Na	110	12.0
80.	Mesitylenecarboxylic	0.01522	iv	40.0 Na	110	12.0

^aAll reaction mixtures were made up with 5 cc. of deuterioalcohol (0.08526 moles). Six different batches of deuterioalcohol were used, the composition of which is given as follows in terms of D₂O content of water of combustion: i = 3.850 mole %; ii = 3.132 mole %; iii = 3.032 mole %; iv = 2.726 mole %; v = 2.603 mole %; vi = 2.390 mole %. In calculating the results, allowance was made for the alcohol removed by the reaction with the sodium.

^bThe experimental procedure varied according to whether the ester or the alcohol was recovered for the analysis and according to the manner of destroying the catalyst. The procedure is referred to as follows; i = ester recovered by salting out; ii = alcohol recovered by distillation, catalyst destroyed by addition of solid CO₂; iii = alcohol recovered by distillation, catalyst destroyed by addition of equivalent amount of P₂O₅; iv = alcohol recovered by distillation, catalyst not destroyed.

^cReaction mixture contained 5 cc. of ethyl benzoate.

^dReaction mixture contained 5 cc. of tetralin.

of concentrated sulphuric acid at room temperature for fifteen minutes, a white solid was obtained. After washing the solid with water, recrystallizing from absolute alcohol, and drying, it melted at 140°C. (uncorrected).

DISCUSSION OF RESULTS

When an exchange reaction between an aliphatic ester and deuterioalcohol is allowed to proceed to equilibrium, the number of exchangeable hydrogen atoms as calculated from the result of the exchange experiment should be equal to the number of alpha hydrogen atoms in the ester. However, it is generally lower, indicating

TABLE 4--Continued

No.	Experimental Procedure	Mole % D ₂ O from Recovered Liquid	Exchange Number	Percentage Exchange	Remarks
79.	11	2.360	0.276	9.2	Calculated for 3 exchangeable hydrogen atoms
80.	1v	2.680	0.094	1.0	Calculated for 9 exchangeable hydrogen atoms

that the energy contents of the hydrogen and corresponding deuterium compounds are slightly different. In these exchange reactions the deuterium shows a slight preference for the alcohol. In the malonic and phenylacetic series the theoretical and observed exchange numbers are in good agreement.

The rate of exchange in a system of deuterioalcohol and aliphatic ester should be proportional to the number of labile hydrogen atoms in the ester, all other conditions being equal. When the experimental results are expressed in the form of percentage completion, the statistical factor is automatically taken care of. The reactivity of an ester could be expressed as a rate constant if constant catalysis were possible, but unfortunately the sodium of the sodium ethylate was precipitated as a complex during some of the exchange reactions, and the calculated rate constants fell off as time progressed.

The rates of exchange of the various aliphatic esters show that the organic radical attached to the alpha carbon has a marked influence on the lability of the alpha hydrogen atoms. Ethyl acetate has the most labile alpha hydrogen atoms in the series, and the substitution of alkyl radicals decreases the lability of the alpha hydrogen atoms as may be seen in the tables. The order of increasing inhibition is as follows: methoxy, methyl ethyl, decyl, cyclohexyl, decahexyl, and isopropyl.

The order of reactivity given by exchange reactions is the same order found by Roberts and McElvain for the rates of information of the beta keto ester in the Claisen condensation.¹ The

¹Roberts, and McElvain, J. Am. Chem. Soc., 59, 2007 (1937).

rates of exchange isobutyric and isovaleric esters were lower than any other aliphatic esters examined. It is a well-known fact that these two esters fail to undergo the Claisen condensation with sodium ethylate as a catalyst, and the low percentage of exchange was anticipated. However, the rate of exchange experiments show no sharp dividing line between those esters which do undergo the Claisen condensation and those which do not. It was noticed that during the course of exchange those esters which are known to undergo the Claisen condensation deposited a white solid, and those which are known not to undergo the Claisen condensation gave no such deposit.

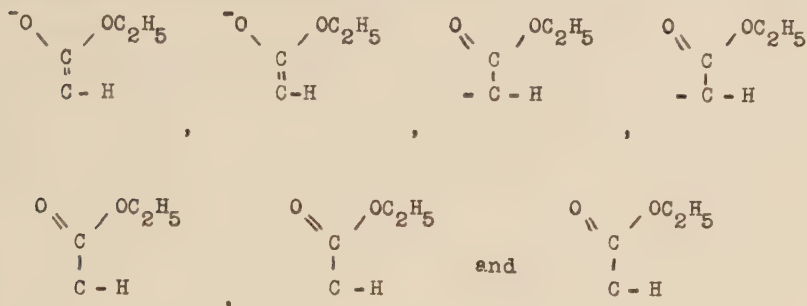
The vinyl group ($-\text{CH}=\text{CH}-$) was found to be capable of transferring the activating effect of a carbonyl group to an adjacent carbon atom which then assumes the rôle of an alpha carbon atom. As the ion of an ester may exist as a composite of three resonating forms, i.e. $\text{R}-\text{CH}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{OC}_2\text{H}_5$ and $\text{R}-\text{CH}=\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{OC}_2\text{H}_5$, the vinyl analogue may be represented in two such limiting forms as $\text{R}-\text{CH}-\text{CH}=\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{OC}_2\text{H}_5$, $\text{R}-\text{CH}=\text{CH}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{OC}_2\text{H}_5$ and $\text{R}-\text{CH}=\text{CH}-\text{CH}=\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{OC}_2\text{H}_5$. Inspection of the results for acetic, crotonic, and sorbic esters indicates that the activating effect of a carbonyl group is successively weakened as it progresses through the vinyl groups to the gamma carbon. The vinyl transference effect is not nearly so noticeable in the cases of o-toluic, p-toluic, and mesitylene-carboxylic esters.

The exchange results are of special interest in the cases of citraconic and mesaconic esters because the alpha hydrogen atoms of the former are much more labile than those of the latter, indicating pronounced steric effects. In connection with these results it may be noted that Coulson and Kon have shown that when either citraconic, mesaconic, or itaconic ester is treated with sodium ethylate, an equilibrium mixture of citraconic, mesaconic, and itaconic esters and the ethoxy addition ester is reached.¹

The lability of the alpha hydrogen atoms in the aromatic substituted acetic esters is much greater than that of the hydrogen atoms in the aliphatic substituted acetic esters. In order to obtain measurable rates of exchange with these esters, the reactions had to be carried out at 0°C . The enhancement of the activating

¹Coulson, and Kon, J. Chem. Soc., 2568-73 (1932).

effect on the alpha hydrogen by the benzene nucleus may be related to the greater number of resonance forms in the corresponding anion, some of which are indicated below.



Further substitution at the alpha position, whether by methyl, methoxy, or by a second phenyl group decreases the lability of the remaining hydrogen atom. The rate of exchange drops to less than half the value for that of phenylacetic ester, and the inhibiting effect is therefore greater than could be accounted for by the statistical factor alone. The fact that the introduction of a second phenyl should bring about a decrease in the lability of the remaining alpha hydrogen atom is surprising and cannot be accounted for on the basis of the number of resonating forms of the ester anion.

The influence of alpha substituents in the malonic ester series is very much the same as in the phenylacetic ester series. Both methyl and phenyl groups decrease the rate of exchange by a factor greater than two. The very high rate of exchange of the compounds in this series could be anticipated in view of the relatively high acid strength of malonic ester ($K_a = 1.2 \times 10^{-8}$).¹ It has been suggested by Johnson² that the greater stability of the enolic anion of a beta dicarbonyl compound may be due to the fact that two of the three resonance forms are identical.

No mention has been made thus far of the fact that sodium ethylate is capable of reacting with esters in another way, namely by addition at the carbonyl group, forming a more or less unstable

¹Vorlaender, *Ber.*, 26, 286 (1903).

²Johnson, in Gilman, "Organic Chemistry," II, 1610.

product of the type supposed by Claisen to be an intermediate in the condensation reaction. The experimental evidence includes the isolation of such addition compounds in a few instances where they happen to be sufficiently stable, as for example, the addition compound of sodium ethylate and the ethyl ester of trifluoroacetic acid, and the analogous compound from methyl benzoate and sodium benzylate. The assumption that this is a general reaction of esters is supported by the fact that the alkoxy group in an ester may be replaced by another on treatment of the ester with a sodium alcoholate, in which reaction it seems necessary to suppose an addition compound as an intermediate. Closely related to this type of reaction is the supposed formation of a similar intermediate by the addition of hydroxyl ion in the hydrolysis of esters by alkali. In order to demonstrate that structural differences in esters do not always influence the two modes of attack in the same way, some of the experimental observations relating to reactions at the carbonyl group will be referred to.

TABLE 5

Ethyl Ester	Comparative Rate of Alkaline Hydrolysis	Percentage Exchange	Conditions of Exchange
Acetic	100.0 ¹	31.6	4 hrs. at 25°C.
Propionic	89.6 ¹	11.8	4 hrs. at 25°C.
Butyric	52.5 ¹	5.7	4 hrs. at 25°C.
Isobutyric	49.2 ¹	1.7	4 hrs. at 25°C.
Isovaleric	25.3 ¹	2.6	4 hrs. at 25°C.
Methoxypropionic ..	(623)	3.1	4 hrs. at 25°C.
Trans-Crotonic	13.7 ¹	21.2	4 hrs. at 25°C.
Phenylacetic	191.0	43.0	5 min. at 0°C.
Hydratropic	14.1 ¹	13.0	5 min. at 0°C.
Methoxyphenylacetic	358.0 ¹	17.3	5 min. at 0°C.
p-Toluic	13.1 ²	9.2	12 hrs. at 110°C.
o-Toluic	6.4 ²	1.5	16 hrs. at 110°C.

¹Olsson, *Z. Physik. Chem.*, **133**, 233 (1922).

²McCombie, and Scarborough, *J. Chem. Soc.*, **107**, 156 (1915).

Referring first to the rates of alkaline hydrolysis (Cf. Table 5) it may be noted that in the series of the esters of acetic, propionic, butyric, isobutyric, and isovaleric acids the rate of hydrolysis decreases in very much the same way as the rate of exchange. If, however, one attempts to include esters which are not

strictly analogous, for example, methoxypropionic ester and phenylacetic ester, the correlation breaks down completely. The phenyl group has a tremendous effect in increasing the rate of exchange, but exerts relatively little effect on the rate of hydrolysis, while for the methoxy group the relationship is quite opposite. However, comparing phenylacetic ester with hydratropic, it will be seen that the structural difference influences both rates in the same way, and this is also true for p-toluic and o-toluic esters.

Further evidence in this direction was obtained by studying the change in optical rotation when the n-butyric, isobutyric, and trimethylacetic esters of optically active secondary butyl carbinol¹ were treated with absolute ethyl alcohol solutions of sodium ethylate. The ratio of ester, alcohol, and sodium used in this experiment was the same as that used in the exchange experiments, and the temperature of the reactions was 26°C. As the esters prepared from the laevo alcohol are dextro-rotatory, the reaction was accompanied by a large change in rotation. In two minutes the n-butyrate alkoxy group exchange was 39% complete, while in the same length of time the isobutyrate reaction was but 8% complete. The rotation of the mixture containing the trimethylacetate did not change in 28 hours. It may be noted that the alkoxy group exchange reactions of the n-butyrate and of the isobutyrate are considerably faster than the corresponding hydrogen exchange reactions.

APPENDIX

Quinone

Quinone was investigated in both acidic and neutral solutions of deuteroalcohol. A sample of commercial quinone was recrystallized from alcohol and carefully dried, this material being used in the subsequent experiments.

One gram of quinone (0.00925 mole) was dissolved in 5 cc. of deuteroalcohol (D₂O on combustion = 3.132 mole %) and placed in a reaction tube. After cooling in a dry ice bath and evacuating, the tube was sealed off, removed from the cooling bath, and placed in an oil bath at 110°C. where it remained for 48 hours. At the

¹This material was prepared by fractional distillation of fusel oil by Mr. W. De Atley and was actually a mixture of active amyl alcohol (65%) and isoamyl alcohol (35 %).

end of this time the tube was removed from the heated bath, cooled to room temperature, and opened. The alcohol in the reaction mixture was removed by careful distillation, and the fraction boiling at 78°C. collected for analysis. The combustion of this alcohol yielded water which contained 2.925 mole % D_2O .

$$\frac{0.03526}{0.00925} \times \frac{3.132 - 2.925}{2.925} = 0.65 \text{ hydrogens exchanged}$$

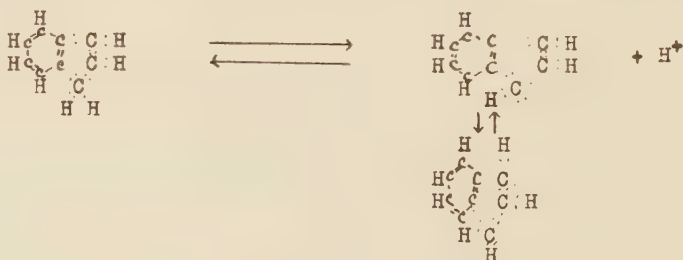
Another reaction mixture was made up containing one gram of quinone, 5 cc. of deuterioalcohol, and 8 milligrams of concentrated sulphuric acid, and treated the same way as was the preceding reaction mixture. Combustion of the alcohol obtained from this reaction mixture yielded a water which contained 2.860 mole % D_2O .

$$\frac{0.03526}{0.00925} \times \frac{3.132 - 2.860}{2.860} = 0.83 \text{ hydrogens exchanged}$$

The results of these reactions were not entirely satisfactory, although it is possible that in a greater length of time higher results might have been obtained. As both of the reaction mixtures darkened under the conditions of the experiment, it was quite apparent that some of the quinone decomposed. There is also the possibility that some of the quinone was reduced by the hot alcohol, and that the indicated exchange was due to the hydroquinone produced.

Indene

As indene has two acidic hydrogens, and as there is electronic symmetry about the beta carbon in the anion of the monosodium salt, it should exchange three hydrogens in the presence of a basic catalyst. The following mechanism is proposed.



Pure indene was prepared as follows.¹ A sample of crude indene from coal tar (B.P. = 175 - 179.5°C.) was treated with an excess of metallic sodium and heated to 125°C. The reaction mixture was then rapidly stirred whilst a stream of ammonia was bubbled into the melt. At the end of 4 1/2 hours the reaction had subsided, and the melt was allowed to cool. The residual globule of sodium was removed from the resinous mass which was in turn heated for several hours in vacuo in order to volatilize unreacted hydrocarbons. The remaining solid was treated with water which liberated the indene. The oil was separated from the aqueous solution and fractionated between 179 - 180°C. The melting point of the product was -2°C (lit M.P. = -2°C.).

As indene slowly polymerizes, and, as the polymer of indene would not necessarily contain exchangeable hydrogen, two reaction mixtures were immediately made up containing the freshly prepared indene. The first reaction mixture was prepared as follows. 40.3 milligrams of sodium were dissolved in 5 cc. of deuteroalcohol (D_2O on combustion = 2.603 mole %), and 0.0423 moles of the purified indene introduced. The color of the reaction mixture immediately became yellow. The reaction mixture was kept in the absence of air at 110°C. for one hour. At the end of this time solid carbon dioxide was added to destroy the catalyst, then the alcohol was distilled from the mixture. The water obtained from the combustion of this alcohol contained 1.154 mole % D_2O .

40.3 milligrams of sodium = 0.00176 gram atoms

0.08526 - 0.00176 = 0.08350 mole of alcohol

$$\frac{0.08350}{0.0423} \times \frac{2.603 - 1.154}{1.154} = 2.48 \text{ hydrogens exchanged}$$

A second reaction mixture was made up by dissolving 35 milligrams of sodium in 4 cc. of deuteroalcohol then introducing 0.0423 mole of indene. This mixture was kept at 24°C. for 19 hours, and at the end of this time solid carbon dioxide was added. The alcohol was recovered by distillation and burned, the water collected analyzing 1.006 mole % D_2O .

35 milligrams of sodium = 0.00152 gram atom

0.06821 - 0.00152 = 0.06669 mole of alcohol

¹Weissgerber, Ber., 42, 569-572 (1909).

$$\frac{0.06669}{0.0423} \times \frac{2.603 - 1.006}{1.006} = 2.50 \text{ hydrogens exchanged}$$

The residue which remained after the removal of the alcohol from the second reaction mixture was extracted several times with water then dried over anhydrous sodium sulphate and distilled. The indene thus recovered was combusted in the usual way yielding a sample of water containing 1.884 mole % D_2O .

$$\begin{array}{rcl} 0.0669 \times 0.1562 & = & 0.010417 \\ 8 \times 0.0423 \times 0.01884 & = & 0.006375 \\ \text{difference} & = & 0.004042 \end{array}$$

$$\frac{0.004042}{\frac{0.06669}{6}} = 1.010 \text{ mole \% } D_2O \text{ from the residual alcohol (calculated)}$$

$$\frac{0.06669}{0.0423} \times \frac{2.603 - 1.010}{1.010} = 2.49 \text{ hydrogens exchanged}$$

At first sight the experimental results could be interpreted to mean that there are either two or three exchangeable hydrogen atoms in the indene molecule. There are however two factors which would give rise to an observed value lower than theoretical. One is the possibility that the indene probably polymerized to a slight extent during the experiment. The other is the fact that our experience in the exchange of aliphatic esters indicated that the equilibrium is such that the deuterium almost always favors the alcohol. The experimental value of 1.95 exchangeable hydrogen atoms was obtained by Heuse,¹ but it seems likely that the indene used in his experiment was of a lesser degree of purity. The new experimental evidence definitely indicates a higher value, namely three exchangeable hydrogen atoms.

SUMMARY

(1) Hydrogen-deuterium exchange experiments were conducted upon acetic ester and its homologues, and malonic ester and its homologues, demonstrating that the number of active hydrogen atoms as calculated from the exchange data approaches the actual number of alpha hydrogen atoms in the ester.

¹Heuse (Unpublished Master's thesis, University of Chicago, 1937).

(2) Rate of exchange experiments were conducted upon these esters under comparable conditions, demonstrating the activating influence of the aromatic alpha substituents and the inhibiting influence of the aliphatic substituents on the lability of the remaining alpha hydrogen atoms.

(3) Rate of exchange experiments were conducted upon acetic, crotonic, and sorbic esters under comparable conditions, demonstrating the decrease in activating effect of the carbonyl group on the "alpha" carbon atom when they are separated by an increasing number of vinyl groups.

(4) A hindrance to the hydrogen-deuterium exchange was observed in experiments on methyl substituted benzoic esters when the methyl groups were ortho in position to the carbethoxy group.

(5) Exchange experiments conducted upon indene lead to the conclusion that there are three exchangeable hydrogen atoms in this compound.

